Remarks

Claims 1, 5, 7, 12, 17, 21, 23, 28, 33, 57, 62, 65, 69, 70, 75, 78, 82, 84, 89, 90, 94, 97, 101, 103, 107, 108, 110, 114, and 119-201 were previously and are still pending in this application. Claims 12, 124, 145, 153 and 163 have been amended to correct typographical errors and/or to clarify claim language. No new matter has been added.

Allowable Claims

Applicants respectfully request clarification of the record. In the Office Actions dated 1/13/04 and 10/20/04, claims 57, 62, 65, 69, 70, 75, 78, 82, 84, 89, 90, 94, 97, 101, 103, 107, 108, 110, 114, 143-187 were "allowed". In addition, claims 28, 122, 127, 132, 133, 137 and 138 were "objected to" only as being dependent on a rejected base claim, but allowable if rewritten in independent form. The new Examiner in the Office Action dated 12/12/2005 appears to have mistakenly overlooked that the status of these claims was "allowed" and "objected to". In particular, the Examiner did not present any new rejection of these claims, but instead simply "maintained" the obviousness rejections of record. The Examiner, however, listed all the claims as rejected. This appears to be in error, as there is no outstanding rejection of the claims previously allowed. Applicants assume that the inclusion of the previously allowed claims in the rejection was an oversight and that the previous status of the above listed claims remains accurate.

Rejections Under 35 U.S.C. §103

The Examiner maintained the obviousness rejection of claims 1, 5, 7, 12, 17, 21, 23, 33, 119-121, 123-126, 128-131, 134-136, 139-142, and 188-201 under 35 U.S.C. 103(a) as being unpatentable over Yoshida et al, Kataoka et al, and Rentsch et al. The Examiner stated the "declaration has been considered and it [does] not overcome the instant 103." The Examiner additionally states, "[a]pplicant's arguments on MTD levels of the prior art are inconclusive because the MTD of the compounds used in the prior art are not presented." Applicants respectfully request reconsideration.

Applicants believe the present rejection is improper because: (1) the Examiner has not met the burden of making a *prima facie* case of obviousness, (2) the cited references, taken

together, actually teach away from the claimed invention, (3) there is additional prior art of record (US patent 5,580,899, Mayhew et al.) discussed below that teaches away from the claimed invention.

The Kataoka et al. reference shows comparative data on a fatty acid conjugate versus the parent compound. Kataoka et al. show an experiment involving a fatty acid-anti cancer drug conjugate, N4-behenoyl-Ara-C. The conjugate was given at a dose of 100-1000 mg/kg, IP. This was then contrasted with the parent compound, Ara-C, which was reported to be given at a dosage of 1600 mg/kg IP. Clearly, the conjugate was given at a ***lower*** dose than the parent compound. Thus, Kataoka et al does not teach administering a fatty acid conjugate at a dose *above* the dose of the parent compound. This is the opposite of that required by the claimed invention. Therefore, Kataoka at al teaches away from the claimed invention.

It is the Examiner's burden to present a reference which suggests the claimed invention. It does not matter whether the MTD of Ara-C IP is higher than 1600 mg/kg IP. It is clear that the 1600 mg/kg dose was used in the model and that the mice tolerated this dose, suggesting that this dose was either at or below the MTD of Ara-C in this model. It also is clear that the dose of the N4-behenoyl-Ara-C conjugate was ***lower*** than 1600 mg/kg IP. Therefore, it is not possible to conclude from Kataoka et al. that a conjugate should be given at a dose above the MTD of the parent compound, as claimed. There is no basis in Kataoka for a *prima facie* case for rejecting the claims.

The outstanding rejection is based on the following position. In the prior action discussing the rejection on the basis of Kataoka et al., the Examiner refers to Kataoka teaching that the conjugate releases the Ara-C over time. The Examiner stated that Kataoka teaches that "the fatty acid endows Ara-C with hydrophobicity and, thus, enables BH-AC to be released slowly in the body and would circulate in the body for a prolonged period of time. From this the Examiner concludes that a *higher* dose of conjugate would be suggested. Such a conclusion, however, is contradicted by the Kataoka et al. reference itself and is counter intuitive.

Kataoka et al. administered the conjugate at a ***lower*** dose than the parent. This confirms what one of ordinary skill in the art would have expected, that is, if the drug circulates for a longer period, then a need for less drug would be expected.

As pointed out in the Declaration by Dr. Balthasar (submitted with the previous response filed on July 12, 2004), the Examiner's conclusion is contradicted by other scientific literature, as well. Dr. Balthasar provided examples from the literature that demonstrated that slow release of anti-cancer drugs, where the time-course of drug circulation is prolonged, can actually decrease MTD. One example cited by Dr. Balthasar, was a review of phase I clinical studies with topotecan, Rowinsky and Verweij cited data showing that the MTD of topotecan is highly dependent on the mode of topotecan administration, ranging from 22.5 $mg/m^2/d$ when released into the body over 30 min, to 1 $mg/m^2/d$ when released into the body over 72 h (Rowinsky EK and Verweij J, Review of phase I clinical studies with topotecan, Seminars in Oncology, 24: S20-3-S20-10, 1997). Thus, *less* drug had to be administered when the drug was administered more slowly.

Another more recent example provided by Dr. Balthasar was from Dr. Balthasar's work showing that slowing the time course of drug administration *decreases* MTD. In recent work conducted in Dr. Balthasar's laboratory (Lobo ED and Balthasar JP, Pharmacokinetic-pharmacodynamic modeling of methotrexate-induced toxicity in mice, Journal of Pharmaceutical Sciences, 92: 1654-1664, 2003), toxicity induced by methotrexate following intra-peritoneal administration in mice was investigated. The MTD of methotrexate was highly dependent on the time-course of release of the drug. For example, following administration of methotrexate by rapid ("bolus") injection, the authors found that MTD was 760 mg/kg. Following slow release of the dose from an osmotic pump over 72 hours, they found that MTD was dramatically reduced to 3.8 mg/kg. Again, *less* drug had to be administered when the drug was administered more slowly.

There is also additional prior art of record (US patent 5,580,899, Mayhew et al.) that teaches away from the claimed invention. Mayhew, teaches that the administration of *less*, not more, of the fatty acid conjugated drug. Mayhew specifically teaches administering the fatty acid conjugated drugs described in Mayhew in amounts that are the *same as* or *less than* the amounts used when administering the unconjugated anticancer compounds. See column 9, lines 50-67 and column 12, lines 52-67. Mayhew makes it clear that the dose of the fatty acid conjugated drug would have been expected to be a reduced dose compared to the dose of the unconjugated drug. Thus, Mayhew teaches away from a main feature of the present invention,

that is, the administration of anticancer compounds as conjugates in amounts which exceed the MTD of the unconjugated anticancer compound.

The remaining cited references do not undermine or contradict this teaching away from the invention. Yoshida et al. investigated the administration of a fatty acid conjugate of Ara-C (BH-AC) which was administered at doses ranging from 500 mg/m^2 to 1300 mg/m^2 by intravenous (IV) drip in 10 patients diagnosed with non-Hodgkin's lymphoma. The dose levels (500, 700, 900, and 1300 mg/m^2) were administered to groups of three patients on a 5-consecutive day schedule. Yoshida et al. did not investigate toxicity resulting from the administration of the parent compound (Ara-C), nor did Yoshida et al. provide pharmacokinetic data on Ara-C administered IV. As such, this reference does not provide a comparison of the MTD of the conjugate versus Ara-C in this treatment group by this mode of administration. Thus, Yoshida et al does not teach anything about the MTD of a conjugate versus a parent compound. Accordingly, it is not possible to conclude from the teachings of Yoshida et al. that fatty acid drug conjugates of Ara-C have a MTD exceeding that of Ara-C . It certainly is not possible to conclude from Yoshida et al. that one can administer a conjugate at an MTD of 100% of the parent MTD, as Yoshida et al. refer to prior art administrations of Ara-C as high as 3 g/m^2 (3,000 mg/m^2, q 12 hours, days -7 to -4; from Champlin et al., Seminars in Oncology, Vol. XII, No. 2, supplement 3, 1985, pages 190-195, cited in Yoshida.)

Applicants point out that it is the Examiner's burden to present a reference upon which a *prima facie* rejection can be based. The Yoshida et al. reference does not represent a such a reference, particularly when taken together with all the references of record which teach away from the invention. Yoshida et al. teach nothing about the MTD of a conjugate versus a parent compound. The Examiner admits as much. Yoshida et al., therefore, cannot be the proper basis for an obviousness rejection. The absence of a suggestion of the present invention by Yoshida et al. must be resolved consistent with the other art of record. The other art of record suggests clearly lower doses of conjugate than that of parent compound. The Examiner should not, and cannot not under the law, ignore the prior art as a whole.

Regarding Rentsch et al., they studied 4-N-octadecyl-Ara-C, an alkylated derivative of Ara-C bearing a saturated C18 alkyl group on the Ara-C 4-amino group (not a fatty acid conjugate). This reference also discloses no comparative data on dose levels of 4-N-octadecyl-

Ara-C relative to dose levels of Ara-C in mice. Rentsch et al, did not investigate the development of toxicity following the administration of Ara-C and/or following administration of the alkylated derivative of Ara-C. Consequently, the teachings of Rentsch et al. do not allow making conclusions about the MTDs of Ara-C and/or conjugates of Ara-C.

In summary, it is clear that none of the references (cited and/or of record) teach or suggest the main and novel feature of the instant invention. On the contrary, the references teach away from the claimed invention. It is not possible to conclude from the cited art that one can administer a conjugate at an MTD, for example, of 100% of the MTD for the parent compound. Moreover, the only reason advanced for rejecting the claims is contradicted by the prior art of record. It, therefore, is believed that the Examiner has not made out a *prima facie* case for rejecting the claims.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. 103.

Rejection on the Basis of Obviousness-type Double Patenting

The Examiner rejected claims 1, 5, 7, 12, 17, 21, 23, 28, 33, 57, 62, 65, 69, 70, 75, 78, 82, 84, 89, 90, 94, 97, 101, 103, 107, 108, 110, 114, 119-201 on the basis of obviousness-type double patenting over claim 7 of U.S. 6,602,902 because the claims are "fully embraced" by the prior art claim 7." Applicants respectfully traverse.

The Examiner has not made out a *prima facie* case for rejecting these claims on the basis of obviousness-type double patenting. The test for obviousness-type double patenting is whether the pending claims would have been obvious over issued claim 7. The test is not whether the pending claims would infringe or be "embraced by" the issued claim. Withdrawal of this rejection is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

A three-month extension of time, from March 12, 2006 to June 12, 2006, is requested for response to the Office Action mailed from the Patent Office on December 12, 2005. A check in the amount of $1,020.00 is enclosed for said extension. If there is any additional fee occasioned by this response, including any additional extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
Webb, et al., Applicant(s)

By: _____

Roque El-Hayek, Reg. No. 55,151
Edward R. Gates, Reg. No. 31,616
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
Telephone: (617) 646-8000

Docket No.: N0260.70031US00
Date: 6/12 /06
x06/12/06x